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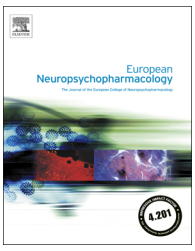

Effect of cariprazine across the symptoms of mania in bipolar I disorder: Analyses of pooled data from phase II/III trials

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Abstract
Bipolar I disorder is a chronic disorder characterized by episodic recurrences of mania, depression, and mixed affective states interspersed with periods of full or partial remission; subsyndromal residual symptoms between episodes are common and disabling. Cariprazine, an atypical antipsychotic, is a potent dopamine D_3 and D_2 receptor partial agonist with preferential binding to D_3 receptors. Post-hoc analyses of pooled data from 3 positive trials were conducted to evaluate the effect of cariprazine 3–12 mg/d on the symptoms of mania in inpatients (18–65 years) with bipolar I disorder and a current manic episode. Analyses were based on the pooled intent-to-treat (ITT) population (placebo=429; cariprazine=608). Mean change from baseline to the end of treatment on individual Young Mania Rating Scale (YMRS) items was analysed using a mixed-effects model for repeated measures (MMRM); categorical symptom severity shifts were analysed using logistic regression. Statistically significant improvement in mean change was seen for cariprazine versus placebo on all 11 YMRS items ($p<0.0001$); significantly more cariprazine- versus placebo-treated patients had mild/no symptoms at the end of treatment on 11 YMRS items ($p<0.0001$) and concurrently on the 4 YMRS core symptoms (irritability, speech, content, and disruptive-aggressive behaviour) ($p<0.0001$). Significantly more cariprazine- versus placebo-treated patients shifted from a Moderate/Worse or Marked/Worse Symptoms categories to Mild/No Symptoms on all 11 ($p<0.0001$) and 9 of 11 YMRS items ($p<0.05$), respectively. Results suggest that cariprazine

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treatment improved mania across YMRS symptoms; a significant percentage of cariprazine- versus placebo-treated patients had mild/no symptoms at the end of treatment.

1. Introduction

Bipolar I disorder is a chronic and disabling disorder characterized by episodic recurrences of mania, hypomania, depression, and mixed affective states interspersed with periods of full or partial remission. The hallmark diagnostic feature of bipolar disorder is a manic episode, which is classically described as a state of euphoria, although intense irritability, agitation, and psychotic features are common (American Psychiatric Association, 2013). Mania is characterized by a broad array of symptoms including grandiosity, mood lability, decreased need for sleep, and cognitive impairment (Leboyer and Kupfer, 2010); patients may also experience psychotic symptoms, impaired functioning, substance abuse, and anxiety disorders (Judd et al., 2005; Sachs et al., 2011). During a manic episode, individuals may not perceive that they need treatment, although consequences of poor judgment, hyperactivity, and lack of insight are severe enough to profoundly impair social and professional functioning or to require hospitalisation.

Between full syndromal affective episodes, the majority of patients with bipolar disorder spend almost 50% of their time unwell due to subsyndromal symptoms that persist after the treatment and resolution of an acute episode (Altshuler et al., 2002; Joffe et al., 2004; Judd et al., 2002; Vieta et al., 2008). Subsyndromal residual symptoms are associated with diminished quality of life, functional impairment, and risk of early relapse and recurrence (Judd et al., 2008; Tohen et al., 2006). Although several pharmacotherapies from various drug classes are approved for the treatment of bipolar mania (Jann, 2014), all agents are not effective in all patients and the high incidence of residual symptoms and recurrence demonstrate the need for additional treatments with strong efficacy across the range of acute symptoms. Comprehensive symptomatic improvement and recovery may improve the occurrence of residual symptoms, helping to decrease relapse and improve overall patient well-being in bipolar disorder.

While controlled clinical trials provide important data about the ability of an agent to reduce manic symptoms, mean change from baseline on a validated rating scale may not be the only outcome measure that is relevant to a clinician treating bipolar disorder. Using procedures adopted from meta-analyses, (Riley et al., 2010) innovative analyses can be conducted on data recorded from individual patients in clinical trials, so called patient-level data. By pooling these data from similarly designed trials to create a single dataset, statistical power is increased compared to the individual studies themselves allowing for patient subgroup analyses, examination of treatment effects across individuals, and adjustment for baseline factors. Unlike aggregate data, which provides averaged or estimated results from across all individuals in a study, patient-level data goes beyond mean change to identify clinically meaningful improvement in individual patients. Recent trends in psychiatric research advocate for finer grain analysis of clinical dimensions and symptoms, so called “molecular psychopathology” (Vieta, 2014), moving away from the broad syndromes and approaching “precision psychiatry” (Vieta, 2015).

Based on positive clinical trial evidence and favourable short-term adverse effect profiles, monotherapy with an atypical antipsychotic agent is a recommended first-line treatment for mania associated with bipolar disorder (Nivoli et al., 2011). Cariprazine, an atypical antipsychotic candidate, is a potent dopamine D_3 and D_2 receptor partial agonist with preferential in vitro binding to D_3 receptors. It is currently being investigated for the treatment of schizophrenia, bipolar mania, bipolar depression, and as an adjunctive treatment for major depressive disorder (MDD). Cariprazine has demonstrated efficacy and tolerability in 3 phase II or phase III clinical trials of adult patients with bipolar I disorder. The primary efficacy parameter in each of these 3 positive studies was change from baseline to week 3 in Young Mania Rating Scale (YMRS) (Young et al., 1978) total score. The YMRS is an 11-item clinician-rated scale that measures the severity of mania symptoms.

Post-hoc analyses of pooled patient-level data from the 3 positive clinical trials were conducted to evaluate the effect of cariprazine on the symptoms of bipolar mania. Analyses included assessments of change on the individual items of the YMRS and the YMRS core items (irritability, speech, content, disruptive/aggressive behaviour), and novel category shift analyses that evaluated the percentage of patients who improved from a more severe level of baseline symptoms to mild or no symptoms at the end of treatment.

2. Experimental procedures

2.1. Study design

Data were pooled from the 3 similarly designed, randomized, placebo-controlled, double-blind, multicenter, parallel-group studies of cariprazine in adult patients with bipolar I disorder; detailed methods of the constituent studies are published elsewhere (Calabrese et al., 2015; Durgam et al., 2015; Sachs et al., 2015). In brief, each study had a washout period of up to 1 week followed by 3 weeks of double-blind treatment and a 2-week safety follow-up period; patients were hospitalised during screening and for a minimum of 2 weeks of treatment. Two of the trials (RGH-MD-31 [NCT00488618] and RGH-MD-32 [NCT01058096]) used flexibly dosed cariprazine 3–12 mg/d; one trial (RGH-MD-33 [NCT01058668]) had a fixed/flexible-dose

design with 2 cariprazine treatment arms (3-6 mg/d or 6-12 mg/d).

2.2. Patients

Male and female inpatients (18-65 years of age, inclusive) with a diagnosis of bipolar I disorder based on *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, text revision (DSM-IV-TR) (American Psychiatric Association, 2000) and an acute manic or mixed episode were included in the constituent studies; patients currently experiencing a first manic episode were excluded. Patients were required to have a YMRS total score ≥ 20, a score ≥ 4 on at least 2 of the 4 core YMRS items, and a Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) total score <18.

Key exclusion criteria were typical of studies conducted in bipolar I disorder and included patients who met the criteria for a principal DSM-IV-TR-based axis I diagnosis other than bipolar I (conduct disorder, obsessive-compulsive disorder, and anxiety disorders were allowed), rapid cycling, substance abuse, or suicide risk defined as a past year attempt, score ≥ 5 on MADRS item 10 (Suicidal Thoughts), or results of psychiatric interview or the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011).

2.3. Post-hoc analyses

Post-hoc analyses were based on the YMRS, a scale that has 4 well-described anchor points for each of its 11 items to grade the severity of the symptom, with higher scores indicating greater severity. On 7 of the items (elevated mood, increased motor activity, sexual interest, sleep, language-thought disorder, appearance, and insight), anchor point scores range from 0 (absence of the symptom or normal, appropriate behaviour) to 4 (most severe). On the 4 core items of the YMRS (irritability, speech [rate and amount], content, and disruptive-aggressive behaviour), anchor points are given twice the weight to compensate for poor cooperation from severely ill patients and the scores range from 0 (absence of the symptom) to 8 (most severe).

Post-hoc outcomes of interest were mean change from baseline to the end of the study on the individual items of the YMRS; the percentage of patients at the end of the study that had mild or no symptoms on all 11 YMRS individual items (score <2 on 0-4 items or <4 on the core items); the percentage of patients at the end of the study that had mild or no symptoms on all 4 core items of the YMRS concurrently (irritability, speech, content, disruptive/aggressive behaviour item scores <4); and the percentage of patients that improved in a novel categorical shift analyses from a more severe symptom category at baseline to a less severe symptom category at the end of the study.

In the categorical shift analyses, evaluations were conducted on each of the 11 individual items of the YMRS (items scored 0-4 or 0-8); a separate analysis was also performed to evaluate shift on the 4 YMRS core items concurrently (items scored 0-8). To quantify a shift, the score for each anchor point description was given a severity rating. On items with a score range of 0-4, a score of 0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=marked symptoms; 4=severe symptoms. On the core items with a score range of 0-8, a score of 0=no symptoms; 2=mild symptoms; 4=moderate symptoms; 6=marked symptoms; 8=severe symptoms. For the shift analysis, severity ratings were then grouped into categories defined as "Mild/No Symptoms" (YMRS score <2 [0-4 items] or <4 [core items]), "Moderate/Worse Symptoms" (YMRS score ≥ 2 [0-4 items] or ≥ 4 [core items]), and "Marked/Worse Symptoms" (YMRS score ≥ 3 [0-4 items] or ≥ 6 [core items]).

The percentage of patients who shifted from a more severe category to a less severe category on each of the 11 individual YMRS items and the percentage of patients who shifted on all 4 YMRS core items concurrently were evaluated using 2 severity criteria. For the first severity criterion, the percentage of patients that shifted from the Moderate/Worse Symptoms category at baseline to the Mild/No Symptoms category at week 3 was evaluated. For the second severity criterion, the percentage of patients that shifted from the Marked/Worse Symptoms severity category at baseline to the Mild/No Symptoms category at week 3 was evaluated.

2.4. Statistical analyses

Analyses were based on the pooled intent-to-treat (ITT) population, which consisted of all patients who received study medication and had ≥ 1 postbaseline YMRS assessment. All cariprazine doses (3-12 mg/d) were pooled for these post-hoc analyses. Mean change from baseline to the end of week 3 on the YMRS individual items was analysed using a mixed-effects model for repeated measures (MMRM), with treatment group, study, study centre within study, visit, and treatment-group-by-visit interaction as fixed effects and baseline YMRS score and baseline-by-visit interaction as covariates; an unstructured covariance matrix was used to model the covariance of within-patient scores. Effect sizes were calculated for changes from baseline on the individual items of the YMRS using Cohen's *d*. YMRS category shift analyses were based on a logistic regression model with study, treatment group, and baseline values as explanatory variables; missing values were imputed using the last observation carried forward (LOCF) approach. Odds ratio (OR) and *p* values were calculated for each comparison of cariprazine versus placebo; *p* values for post-hoc analyses were not adjusted for multiple comparisons. All statistical tests were 2-sided at the 5% significance level.

3. Results

3.1. Patient disposition and baseline characteristics

A total of 1065 patients received double-blind treatment in the 3 studies (pooled safety population); 1037 patients in the safety population additionally had a valid postbaseline YMRS assessment and comprised the pooled ITT population (placebo=429; cariprazine=608). Demographic and baseline characteristics for the pooled population are presented

Table 1 Demographic and baseline characteristics (pooled ITT population).

Characteristics	Placebo $n=429$	Cariprazine 3-12 mg/d $n=608$
Age, mean (SD), years	39.0 (11.6)	39.7 (11.7)
Men, *n* (%)	259 (60)	358 (59)
Race, *n* (%)		
White	201 (47)	309 (51)
Black	102 (24)	163 (27)
Asian	116 (27)	125 (21)
Other	10 (2)	11 (2)
Weight, mean (SD), kg	77.5 (19.2)	77.5 (19.0)
Body mass index, mean (SD), kg/m^2	27.0 (5.7)	27.0 (5.7)
Psychiatric history		
Bipolar I duration, mean (SD), years	12.9 (9.0)	13.4 (9.8)
Duration of current episode, % of patients		
$\leq$7 days	11	11
8-14 days	41	39
15-21 days	15	17
$>$21 days	33	34

ITT indicates intent-to-treat.

Table 2 Severity of symptoms in the pooled population at baseline (pooled ITT population).

YMRS individual items	Treatment groups	*n*	Baseline score, mean (SD)	Moderate/worse baseline severity, *n* (%)	Marked/worse baseline severity, *n* (%)
Elevated mood	Placebo	429	2.9 (0.8)	416 (97.0)	325 (75.8)
	Cariprazine	608	3.0 (0.8)	581 (95.6)	474 (78.0)
Increased motor activity-energy	Placebo	429	2.9 (0.7)	414 (97.0)	347 (80.9)
	Cariprazine	608	2.9 (0.7)	590 (97.0)	505 (83.1)
Sexual interest	Placebo	429	1.5 (1.2)	233 (54.3)	96 (22.4)
	Cariprazine	608	1.8 (1.2)	375 (61.7)	189 (31.1)
Sleep	Placebo	429	2.6 (0.9)	387 (90.2)	255 (59.4)
	Cariprazine	608	2.6 (0.8)	556 (91.4)	396 (65.1)
Irritability[a]	Placebo	429	4.2 (1.3)	351 (81.8)	75 (17.5)
	Cariprazine	608	4.3 (1.3)	503 (82.7)	114 (18.8)
Speech[a]	Placebo	429	4.7 (1.3)	386 (90.0)	138 (32.2)
	Cariprazine	608	4.7 (1.4)	549 (90.3)	199 (32.7)
Language-thought disorder	Placebo	429	2.4 (0.6)	403 (93.9)	179 (41.7)
	Cariprazine	608	2.4 (0.6)	572 (94.1)	259 (42.6)
Content[a]	Placebo	429	4.9 (2.0)	332 (77.4)	202 (47.1)
	Cariprazine	608	4.8 (1.9)	474 (78.0)	254 (41.8)
Disruptive-aggressive behaviour[a]	Placebo	429	3.2 (1.5)	209 (48.7)	23 (5.4)
	Cariprazine	608	3.3 (1.4)	303 (49.8)	32 (5.3)
Appearance	Placebo	429	1.3 (1.0)	175 (40.8)	46 (10.7)
	Cariprazine	608	1.4 (1.0)	267 (43.9)	88 (14.5)
Insight	Placebo	429	1.2 (1.3)	153 (35.7)	90 (21.0)
	Cariprazine	608	1.3 (1.4)	242 (39.8)	151 (24.8)

ITT indicates intent-to-treat; YMRS, Young Mania Rating Scale.

[a]Indicates the core items of the YMRS (score range of 0-8; 0=no symptoms; 2=mild; 4=moderate; 6=marked; 8=severe; for YMRS items other than core items, the score range is 0-4 (0=symptoms; 1=mild; 2=moderate; 3=marked; 4=severe). Moderate/worse severity indicates YMRS score $\geq$2 (0-4 items) or $\geq$4 (core items); Marked/Worse Severity indicates YMRS score $\geq$3 (0-4 items) or $\geq$6 (core items).

in Table 1. The majority of the patients were men, the mean age was 39-40 years, and the mean duration of bipolar I disorder was 12-13 years.

Mean (SD) baseline scores on the YMRS individual items were similar between cariprazine- and placebo-treatment groups (Table 2). When baseline scores were grouped into

Moderate/Worse severity (score ≥ 2 [0-4 items] or ≥ 4 [core items]) or Marked/Worse Severity (score ≥ 3 [0-4 items] or ≥ 6 [core items]) categories, this patient population was shown to be highly symptomatic (Table 2). Moderate or worse baseline severity was seen in $\geq 90\%$ of patients on the YMRS items of elevated mood, increased motor activity-energy, sleep, language-thought disorder, and speech, and in $>50\%$ of patients on the items of sexual interest, irritability, and content; approximately 50% of patients also had moderate or worse severity on the disruptive-aggressive behaviour item. Marked or worse baseline severity was present in more than half of patients on the YMRS items of elevated mood, increased motor activity-energy, and sleep; the percentage of patients with marked or worse baseline severity on the core YMRS disruptive-aggressive behaviour item was low (5%). The ability to analyse the groups with marked or worse baseline severity was hampered by small numbers of patients in some of the symptom domains.

4. YMRS item analyses

4.1. Individual items

Significant improvement in mean change from baseline to week 3 was seen on all 11 individual YMRS symptom items in favour of cariprazine versus placebo (Figure 1). Substantial treatment effects (Cohen's *d*) in favour of cariprazine versus placebo were seen on all YMRS single items (Figure 2); the largest effect sizes for cariprazine treatment were noted on the irritability (0.55) and disruptive-aggressive behaviour (0.49) items.

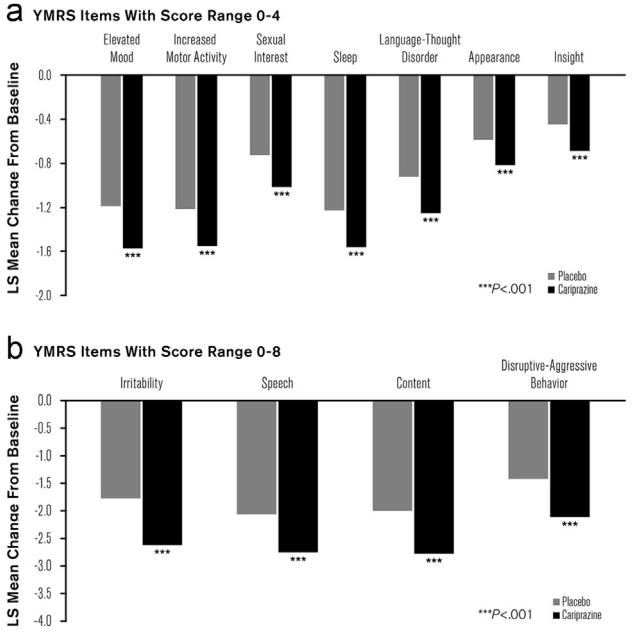

Figure 1 *YMRS individual items: mean change from baseline to week 3 in the pooled ITT population* (*MMRM*). The difference in mean change was statistically significant in favour of cariprazine on all individual YMRS items. ***$p<0.001$.
Note: YMRS indicates Young Mania Rating Scale.

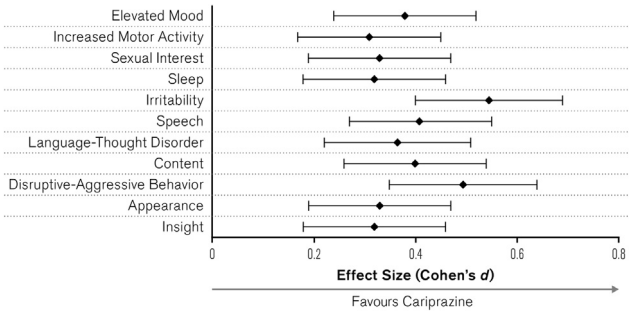

Figure 2 *YMRS single items: cariprazine effect sizes* (*pooled ITT population, MMRM*). Effects sizes (Cohen's *d*) for cariprazine versus placebo on the YMRS single items ranged from 0.31 (increased motor activity) to 0.55 (irritability).
Note: YMRS indicates Young Mania Rating Scale.

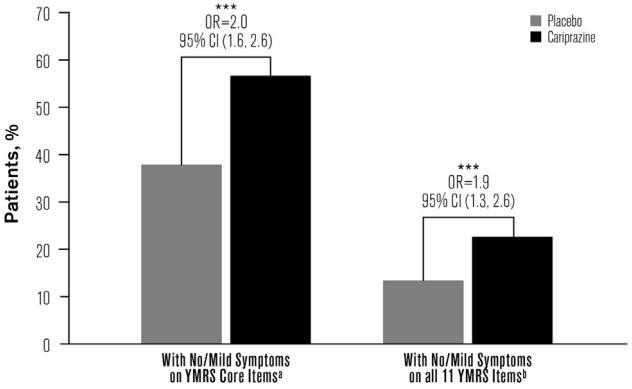

Figure 3 *Percentage of patients with mild or no symptoms on the YMRS at the end of double-blind treatment*. [a]Score <4 on the core items of the YMRS (irritability, speech, content, and disruptive-aggressive behaviour); [b]score <2 (0-4 items) or <4 (core items) on all individual YMRS items. CI indicates confidence interval; OR, odds ratio; YMRS, Young Mania Rating Scale. ***$p<0.001$.

At the end of double-blind treatment, a significantly higher percentage of cariprazine-treated patients than placebo-treated patients had mild or no symptoms (score <2 [0-4 items] or <4 [core items]) on all 11 YMRS items (OR versus placebo=1.9; $p<0.0001$) (Figure 3). A significantly higher percentage of cariprazine-treated patients than placebo-treated patients also had mild or no symptoms (score <4) concurrently on the 4 YMRS core items (irritability, speech, content, disruptive-aggressive behaviour) (OR versus placebo=2.0; $p<0.0001$) (Figure 3).

4.2. YMRS category shift analyses

The percentage of patients that shifted from the Moderate/Worse Symptoms category at baseline to Mild/No Symptoms at the end of double-blind treatment was significantly higher for cariprazine versus placebo on all 11 YMRS individual items (Figure 4). The effects of cariprazine as shown by the odds ratio versus placebo for shifts on these items ranged from 1.6 (increased motor activity-energy) to 2.7 (irritability).

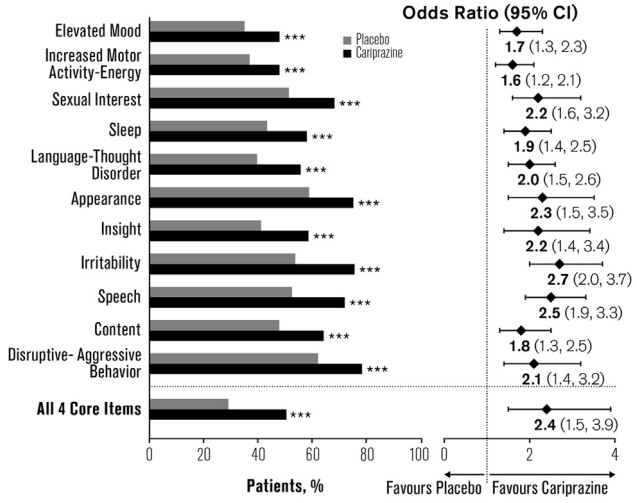

Figure 4 *Percentage of patients in the Moderate/Worse Symptoms category at baseline that shifted to Mild/No Symptoms at the end of double-blind treatment in the pooled ITT population*. Moderate/worse was defined as score ≥ 2 (0-4 items) or ≥ 4 (core items); mild/no symptoms was defined as score <2 (0-4 items] or <4 (core items). YMRS indicates Young Mania Rating Scale. ***$p<0.0001$.

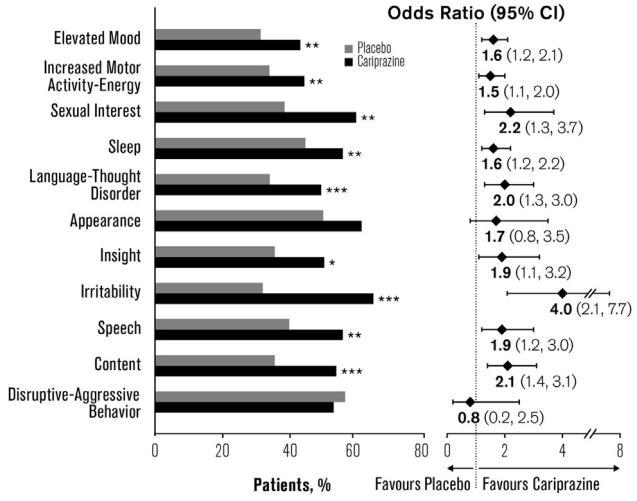

Figure 5 *Percentage of patients in the Marked/Worse Symptoms category at baseline that shifted to Mild/No Symptoms at the end of double-blind treatment in the pooled ITT population*. Marked/Worse was defined as ≥ 3 (0-4 items) or ≥ 6 (core items); mild/no symptoms was defined as <2 (0-4 items) or <4 (core items) at the end of double-blind treatment. YMRS indicates Young Mania Rating Scale. *$p<0.05$; **$p<0.01$; ***$p<0.001$.

Shift from the Marked/Worse Symptoms category to Mild/No Symptoms at the end of double-blind treatment occurred in a significantly greater percentage of cariprazine- versus placebo-treated patients on 9 of 11 YMRS items (Figure 5); the difference in the percentage of cariprazine- and placebo-treated patients who shifted to Mild/No Symptoms was not statistically significant on the appearance or disruptive-aggressive behaviour items. Because a lower percentage of patients were markedly impaired at baseline on the appearance (13%) and disruptive-aggressive behaviour (5%) items compared with other individual items (18-82%), this may have limited the ability to detect a between-group difference on these items. The greatest cariprazine treatment effect as shown by the odds ratio versus placebo was seen on the irritability item, where more than twice as many cariprazine patients (65%) as placebo patients (32%) shifted from Marked/Worse Symptoms to Mild/No Symptoms.

When concurrent shift on the 4 core YMRS items was analysed, the percentage of patients who improved from the Moderate/Worse Symptoms category to Mild/No Symptoms category at week 3 was significantly greater in the cariprazine group (50.5%) than in the placebo group (29.1%) (OR versus placebo, 2.4 [1.5, 3.9], $p=0.0002$). No analyses could be conducted for concurrent shift on the 4 core YMRS items using the Marked/Worse Symptoms to Mild/No Symptoms severity shift criterion. The percentage of patients with marked or worse symptom severity at baseline was only high enough to evaluate on 3 of the 4 core YMRS items (44%, 33%, 18% for content, speech, irritability, respectively); due to the low percentage of patients with marked or worse symptom severity on the disruptive-aggressive behaviour item (5%), concurrent shift of all 4 items was not evaluable.

5. Discussion

Post-hoc analyses conducted on pooled patient-level data from 3 cariprazine studies in adult patients with acute mania associated with bipolar I disorder demonstrated improvement across the spectrum of symptoms associated with bipolar mania in patients treated with cariprazine. Statistically significant improvement for cariprazine versus placebo was seen in mean change from baseline on all 11 individual symptoms of the YMRS; significantly more cariprazine-treated patients also had mild or no symptoms on all YMRS items and on the 4 YMRS core items concurrently at the end of double-blind treatment. In novel categorical shift analyses, greater percentages of cariprazine-treated patients than placebo-treated patients improved from a more severe YMRS symptom category at baseline to the Mild/No Symptoms category at the end of treatment.

Acute mania is often considered a medical emergency, with cognitive, behavioural, and psychotic features contributing to the patient's disability and the necessity to ensure their safety (Grande and Vieta, 2015). However, acute affective episodes do not account for the total morbidity in bipolar disorder since subsyndromal residual symptoms greatly contribute to impaired functioning, diminished quality of life, and faster time to relapse (Altshuler et al., 2002; Joffe et al., 2004; Judd et al., 2008; Marangell et al., 2009; Perlis et al., 2006; Tohen et al., 2006; Vieta et al., 2008). Residual symptoms that remain after an acute manic episode is considered resolved are a clinically useful predictor of bipolar relapse and a robust correlate of a more persistent course of illness (Judd et al., 2008). Treatment with an agent that has broad efficacy across symptoms may help patients achieve symptom-free status, which could lead to more persistent affective stability.

All atypical antipsychotics, except lurasidone and iloperidone, have demonstrated efficacy in treating acute mania (Jann, 2014; Nivoli et al., 2011). In spite of this apparent class effect in bipolar mania, atypical antipsychotic agents have different mechanisms of actions, suggesting that there is a potential for individual differences among agents for treating mania. To date, there is uncertainty surrounding which specific pharmacologic activities drive efficacy in mood disorders (Horacek et al., 2006; Yatham et al., 2005) and the hypothesis that atypical antipsychotic agents may have antimanic differences is supported by the observation that efficacy differences exist when these agents are used to treat bipolar depression (Jann, 2014).

Cariprazine is a potent dopamine D_3 and D_2 receptor partial agonist that has preferential binding to D_3 receptors (Kiss et al., 2010; Slifstein et al., 2013). At antipsychotic-like effective doses, cariprazine shows high and balanced occupancy at D_3 and D_2 receptors (Gyertyan et al., 2011; Kiss et al., 2010) in contrast to other atypical antipsychotics that display high occupancy at D_2 receptors with lower or negligible occupancy at D_3 receptors (Graff-Guerrero et al., 2009; Gyertyan et al., 2011; Mizrahi et al., 2011). The D_3 receptor is thought to play a role in the modulation of cognition and mood (Cho et al., 2010; Laszy et al., 2005) and blockade of this receptor may translate into benefits in treating the broad symptoms associated with bipolar disorder (Beaulieu et al., 2007; Joyce and Millan, 2005; Schwartz et al., 2000). Since different atypical antipsychotic receptor profiles may translate into differences in efficacy and tolerability profiles, examining the effects of cariprazine on the individual symptoms of mania may extract information that elucidates subtle differences for this agent to help inform clinical decision-making according to the symptom profile of individual manic patients.

Deconstructing an acute manic episode into individual symptom components may be a clinically useful way to assess patient status at baseline and at the end of acute treatment, potentially providing information that could enable a clinician to better manage minor, subsyndromal, or residual symptoms between episodes, and in specific subsets of patients. In our pooled analysis population, at least 50% of patients had moderate or worse baseline symptoms on all 11 YMRS items; marked or worse symptoms were also observed for more than half the patients on several items. Of note, more than 90% of patients had at least a moderate baseline level of elevated mood and increased motor activity, which are classic presenting features of mania, while over 80% also presented with high levels of irritability.

When mean change from baseline to week 3 on the YMRS individual items was evaluated, statistically significant differences in favour of cariprazine over placebo were observed on every item, indicating improvement across the spectrum of symptoms associated with bipolar mania. Robust effect sizes for cariprazine were noted on most YMRS individual items (effect size range, 0.31–0.55). The strongest effect for cariprazine treatment was seen on the irritability item, which is an important consideration since many patients experience irritability as a predominant presenting feature in patients with acute mania (American Psychiatric Association, 2013) or mania with depressive symptoms (Vieta et al., 2014). Although few studies using patient-level data to evaluate symptom change in bipolar mania have been reported, it is interesting to note that the effect sizes seen for cariprazine on the individual YMRS items in our analysis were comparable to the effect sizes seen in a post-hoc analysis of YMRS individual items for quetiapine (effect sizes range, 0.24–0.57) (McIntyre et al., 2007).

Since stable recovery in bipolar disorder can only be achieved if patients reach an asymptomatic status (Judd et al., 2008), aggressively targeting and monitoring symptom improvement during treatment may offer an opportunity to improve long-term patient outcomes. Given our highly symptomatic patient population at baseline, it is notable that the odds of cariprazine-treated patients reaching mild or no symptom status at the end of treatment on all 11 YMRS items and on the 4 core items of mania concurrently were 2 times that of placebo-treated patients. This finding suggests that treatment of acute manic episodes with cariprazine may help patients achieve a relatively asymptomatic state that may benefit functioning and decrease risk of relapse during periods of remission.

The YMRS category shift analyses provided opportunities to evaluate patient-level data for clinically meaningful improvement in individual symptoms over the course of treatment. In the Moderate/Worse Symptoms category, a significantly greater percentage of cariprazine- versus placebo-treated patients improved to Mild/No Symptoms on all 11 YMRS individual items, suggesting that cariprazine patients with this level of symptom severity experienced clinically relevant improvement across the range of manic symptoms during the course of treatment.

In the Marked/Worse Symptoms category, a significantly greater percentage of cariprazine-treated patients versus placebo-treated patients shifted to Mild/No Symptoms on 9 of 11 YMRS items, suggesting that cariprazine-treated patients with more severe baseline impairment also experienced improvement in multiple symptoms. The difference in the percentage of cariprazine- and placebo-treated patients who switched to the Mild/No Symptoms category was not statistically significant on the YMRS items of appearance and disruptive-aggressive behaviour, which may have been because the low percentage of patients with baseline marked impairment on these items affected the ability to detect a between-group difference. The small percentage of patients with high baseline scores on the core item of disruptive-aggressive behaviour may have additionally reflected an inability to cooperate with study procedures (e.g., failure to sign the informed consent form, which would have prevented further study participation) for patients with greater illness severity. Alternatively, if rescue medication, such as a benzodiazepine, was required for patients with more severe disruptive or aggressive behaviour, between-group efficacy differences could have been blunted since rescue medication was delivered to patients whether they were on drug or placebo.

Similar to the large effect size seen in mean change from baseline on the YMRS irritability item, the odds of shifting from the Moderate/Worse or Marked/Worse Symptoms categories to the Mild/No Symptoms category was greatest for cariprazine versus placebo on the irritability item, an essential diagnostic feature for mania. In patients with moderate or worse irritability at baseline, the odds ratio for cariprazine-treated patients were 2.7 times higher than placebo-treated patients to shift to the Mild/No Symptoms category at the end

of treatment; in patients with marked or worse baseline severity, the odds of shifting to the Mild/No Symptoms category were even greater (OR [95% CI])=4.0 [2.1, 7.7]).

When concurrent shift in the 4 core YMRS items was analysed in the Moderate/Worse Symptoms category, 51% of cariprazine patients compared with 29% of placebo patients improved to Mild/No Symptoms at end of treatment (p=0.0002). These results suggest that clinically relevant improvement occurred in a significantly greater proportion of cariprazine- than placebo-treated patients on these key items. Although an analysis was planned to evaluate concurrent improvement on the core items in patients in the Marked/Worse Symptom category, it was not conducted because the percentage of patients with a marked or worse score on the disruptive–aggressive behaviour item was too low to evaluate. Potential reasons for the low percentage of patients with marked or worse baseline impairment in disruptive–aggressive behaviour have been discussed previously.

The percentage of patients who shifted from the Moderate/Worse Symptom category at baseline to the Mild/No Symptoms category on the 4 core YMRS items (placebo=29%; cariprazine=51%) may be analogous to the predefined criteria for remission used in the constituent studies (YMRS $\leq$12). The validity of the shift data in relation to the concept of remission is supported by the similarity with remission rates for placebo (30%) and cariprazine (46%) from a previous post-hoc pooled analysis of data from the same 3 constituent studies (Yatham et al., 2015). To put these earlier data into a broader context, when using the YMRS $\leq$8 remission criterion, which is similar to one recommended by the International Society for Bipolar Disorders (YMRS $<$8) (Tohen et al., 2009), remission rates of 19% for placebo and 30% for cariprazine were found (Yatham et al., 2015). The lower rates of remission using this more stringent cut-off may reflect the short duration of these trials since improvement of this magnitude may take longer than 3 weeks to occur.

The concept of remission implies that symptoms of the specified condition, in this case bipolar mania, are absent or nearly absent, and there has not been a concomitant increase in symptoms of another condition (e.g., depression). As such, it is noteworthy that a significantly greater percentage of cariprazine-treated patients (23%) relative to placebo-treated patients (14%) had mild or no symptoms on all 11 YMRS items at endpoint in these post-hoc analyses. Given our highly symptomatic population at baseline, these findings, coupled with the percentage of patients shifting to a less severe level of symptoms concurrently on all 4 core YMRS items, may reflect a multifaceted standard of remission and be one of the more interesting indications of clinically meaningful improvement and a true asymptomatic state.

Limitations of these analyses included their pooled, post-hoc nature and lack of active comparator, suggesting that results should be interpreted accordingly. In addition, the constituent studies were of short duration so the full effect of cariprazine may not have been established and they were not powered to detect treatment differences in individual symptoms. Conventional p values without adjustment for multiple comparisons were used in the post-hoc analyses and although this is typical in post-hoc analyses, random chance may have played a role in determining statistically significant differences. Patients with bipolar II disorder, rapid cycling, and significant depressive symptoms were excluded from participation in the constituent studies; as such, the ability to generalise these findings to other populations on the bipolar spectrum is limited.

Evaluating patient-level data and individual symptom improvement may help inform clinical decision making and tailor treatment strategies in acute bipolar mania. In these post-hoc analyses, treatment with cariprazine relative to placebo improved individual symptoms associated with acute mania and resulted in a statistically greater percentage of patients with mild or no symptoms at the end of treatment. Additionally, novel category shift analyses showed that more cariprazine- than placebo-treated patients shifted from a more severe category of baseline symptoms to a Mild/No Symptoms category at end of treatment. Collectively, results from these analyses suggest that cariprazine had broad efficacy across the individual symptoms of acute mania and treatment may result in clinically relevant improvement for adult patients with bipolar I disorder.

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Contributors

Eduard Vieta was involved in the design of the analyses, interpretation of data, and review of the manuscript.

Suresh Durgam was the medical director for the studies that were included in the analyses and was involved in the design of the analyses, interpretation of data, and review of the manuscript.

Kaifeng Lu conducted the statistical analyses and was involved in the interpretation of data and review of the manuscript.

Adam Ruth was involved in the design of the analysis, interpretation of data, literature searches, and preparation of the initial draft of the manuscript.

Marc Debelle was involved in the interpretation of data and review of the manuscript.

Stephen Zukin was involved in the design of the analysis, interpretation of data, and review of the manuscript.

All authors contributed to and have approved the final manuscript.

Conflict of interest

Suresh Durgam, Kaifeng Lu, and Stephen Zukin acknowledge a potential conflict of interest as current or former employees of Forest Research Institute, an Allergan affiliate. Marc Debelle acknowledges a potential conflict of interest as an employee of Gedeon Richter Plc. Adam Ruth acknowledges a potential conflict of interest as a former employee of Prescott Medical Communications Group, Chicago, IL, a contractor of Forest Research Institute, an Allergan affiliate.

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